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# Hemodynamic safety and efficacy of ferumoxytol as an intravenous contrast agents in pediatric patients and young adults

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ABSTRACT

*Purpose:* To evaluate the safety and feasibility of off-label use of ferumoxytol as an intravenous MRI contrast agents in pediatric patients and young adults.
*Materials and methods:* With HIPAA compliance and IRB approval, 86 consecutive patients who had undergone 3 T or 1.5 T MRI with ferumoxytol were retrospectively identified. The blood pressure and heart rate of patients before and after ferumoxytol injection were compared. The overall image quality was evaluated independently by two radiologists with a four-point scale. Interobserver agreement was calculated using weighted kappa statistics.
*Results:* The mean ± standard deviation (SD) pre and post-contrast systolic blood pressures (SBP) were 101 ± 18 and 95 ± 20, respectively. There was a statistically significant difference between pre-SBP and post-SBP ($P = 0.003$). The pre-contrast diastolic blood pressure (DBP) and the post-contrast diastolic blood pressure (DBP) were 60 ± 14 and 51 ± 17, respectively. There was a statistically significant difference between pre-DBP and post-DBP ($P < 0.001$). The number of patients with SBP and DBP increase, SBP increase and DBP decrease, SBP decrease and DBP increase, SBP and DBP decrease, SBP increase and DBP unchanged were 14 (16%), 9 (10%), 6 (7%), 56 (65%), 1 (1%), respectively. There was moderate agreement on all individual assessments of image quality (kappa = 0.45). Eighty-two of 86 (95.4%) studies were scored 3 or above (at least diagnostic quality) by both readers, with 90% confidence interval of 92–99%.
*Conclusion:* Ferumoxytol is effective as an MR contrast agent. In our sample, there was on average a small but clinically insignificant drop in SBP and DBP post-contrast injection. Large, randomized, controlled trials are needed to establish optimal dosing, imaging procedures, and safety monitoring.


## 1. Introduction

Ferumoxytol is a superparamagnetic iron oxide nanoparticle (USPIO) approved in 2009 by the FDA for treatment of iron deficiency anemia (IDA) in adults with chronic kidney disease (CKD) [1]. However, it also has T1, T2, and T2* shortening properties on magnetic resonance imaging (MRI) [2], and has been investigated extensively as an intravenous contrast agent. Some recent reports have suggested the potential role of ferumoxytol as an alternative to gadolinium-based contrast agents (GBCAs) in adult patients with CKD [3,4]. Ferumoxytol can be administered as a rapid bolus with a rate of up to 1 mL/s and has a long intravascular half-life on the order of 14–15 hours, and a standard therapeutic dose can affect MRI for days to months [5]. This long blood-pool residence time is facilitated by a carbohydrate (carboxymethyl dextran) coat, which prolongs the intravascular residence time and decreases leakage into the extravascular space. The size of the crystal core (6.4–7.2 nm), hydrodynamic size (28–32 nm) and relaxivity values as well ($r1 = 38\ mM^{-1}\ s^{-1}$ and $r2 = 83\ mM^{-1}\ s^{-1}$ at 0.47 T and 39 °C and 40 °C respectively) [6]. In a pediatric setting, the long residence time may be advantageous for repeat sequence acquisition in relatively uncooperative children or for a prolonged acquisition to reduce motion artifacts by signal averaging. All these properties suggest that ferumoxytol could be a useful vascular imaging contrast agent [7,8].

In therapeutic trials, ferumoxytol administration has been associated with an adverse event rate of 5.2% vs. 4.5% for placebo, with the most common adverse events being nausea, dizziness, and diarrhea [9]. A few more serious reactions, particularly hypotension and anaphylaxis, have been reported [10,11]. Ferumoxytol, when used for the management of iron deficiency anemia, is associated with the highest number of reported serious adverse events and other major AEs, among IV iron products. Based on FDA data, the rates of adverse events ranged from 5.24/million units with iron

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sucrose to 745.76/million units with ferumoxytol [10]. In the clinical studies, serious hypersensitivity reactions and hypotension were reported in 0.2% (3/1726) and 1.9% (33/1726) of subjects receiving ferumoxytol, respectively [12]. However, these adverse event rates were reported based on therapeutic dosages of ferumoxytol administered at a rate of 1 mL/s. Usually, the recommended clinical dose is 510 mg IV (i.e. one vial of 17 mL) followed by a second similar dose 3–8 days later. For MRI procedures, usual doses are 1–4 mg/kg [13]. To our knowledge, the literature on the safety and efficacy of ferumoxytol on children undergoing MRI is sparse. However, two recent studies mention the safety of the ferumoxytol in children undergoing MRI, each with less than 9 cases [14,15]. Thus, the purpose of this article is to assess retrospectively our experience with the off-label use of ferumoxytol as a pediatric MRI contrast agent.

## 2. Materials and methods

### 2.1. Subjects

With HIPAA compliance and IRB approval, we retrospectively identified 86 consecutive patients (48 males and 38 females) who underwent contrast-enhanced MRI of the brain, chest, abdomen, pelvis, extremities, spine, and/or heart using ferumoxytol at our pediatric institution between May and December 2014. A chart review was performed to record vital signs (blood pressure and heart rate), clinical indications, field strength, receiver coil, ferumoxytol dose, injection rate, sedation/anesthesia type, and any complications.

### 2.2. Image assessment

All the exams were assessed for overall image quality by two radiologists with five years and eight years of experience. The assessment of the overall image quality of the ferumoxytol-enhanced MRI was performed by using a four-point scale in which a score of 1 indicated that the study was nondiagnostic (the study would not be clinically useful; no diagnosis could be made with the images); a score of 2 that the study was fair (some useful information was provided; the study could be sufficient in some ways for making a diagnosis); a score of 3 that the study was good (clinically useful information was provided; the study was sufficient to make a diagnosis); and a score of 4 that the study was excellent (the study was definitely clinically useful and enabled a confident diagnosis), an approach that has been previously described [16]. Weighted kappa coefficients were calculated to analyze inter-observer agreement between the two readers and interpreted according to the criteria detailed in Table 1. A 90% confidence interval for the proportion of cases with at least diagnostic image quality was calculated.

### 2.3. Vital signs

The pre-contrast blood pressure (pre-BP), the post-contrast blood pressure (post-BP), the pre-contrast heart rate (pre-HR) and the post-contrast heart rate (post-HR) of the subjects were identified. The BP and HR were recorded before and after the administration of ferumoxytol every 10 minutes until the vital signs stable. Usually, the recovery time of patients is 30 minutes. The change in blood pressure was assessed in three ways. First, the difference in SBP and DBP before and after the administration of ferumoxytol was assessed using a two-tailed paired *t*-test, with P value of 0.05 defined as the criterion for statistical significance. Second, the magnitude of BP change was divided into 6 groups (<20%, 20–40%, 40–60%, 60–80%, 80–100% and ≥100%), and the frequency of each group was assessed. Finally, the change in blood pressure was divided into five categories depending on how systolic and diastolic blood pressures changed and the frequency of each category was assessed.

**Table 1**
The interpretation of weighted kappa coefficients.

| Kappa | Interpretation |
|---|---|
| <0 | Poor agreement |
| 0.0–0.20 | Slight agreement |
| 0.21–0.40 | Fair agreement |
| 0.41–0.60 | Moderate agreement |
| 0.61–0.80 | Substantial agreement |
| 0.81–1.00 | Almost perfect agreement |

## 3. Results

Patient ages ranged from 1 day to 34 years (mean ± SD age 7.79 ± 6.66 years). There were 5 adult patients (ages 19, 19, 22, 25, and 34 years, respectively) who underwent ferumoxytol contrast-enhanced MRI at our pediatric institution. The weight ranged from 1.1 to 110.8 kg (mean ± SD weight 29.80 ± 22.67 kg). For all subjects, ferumoxytol was injected at a dose of 0.1 mL/kg (3 mg Fe/kg), and the average volume of ferumoxytol injected was 2.98 mL (range 0.11–11.08 mL). Ferumoxytol was diluted to 10 mL with sterile normal saline, and there was no dilution if the volume of ferumoxytol was more than 10 mL. The ferumoxytol was administered at rate of at most 1 mL/s and flushed with 10 mL of normal saline.

The distribution of cases was 10 (12%) brain, 20 (23%) abdomen/pelvic, 50 (58%) cardiac, 5 (6%) extremity, and 1 (1%) spine. The clinical indications are listed in Table 2.

Five patients underwent 1.5-T MRI scans (Optima MR450w; GE Healthcare, Waukesha, WI) and the remainder underwent 3-T MRI scans (Discovery MR750; GE Healthcare, Waukesha, WI) with different coils (32-channel cardiac, 32-channel torso, 16-channel flexible extremity, 8 channel brain, spine array, run off array) according to the clinical indication. Fifty-eight (67%) patients underwent sedation or general anesthesia (GA) with different types of respiratory support [53 LMA (laryngeal mask); 2 NC (nasal cannula); 3 ETT (endotracheal tube)]. The remaining patients were scanned without sedation.

The SBP, the DBP, and the heart rate (HR) of the patients before and after the injection of ferumoxytol are detailed in Table 3. There was no significant change in heart rate, but a change in diastolic

**Table 2**
Clinical indications.

| Anatomy | Clinical indication | Subjects |
|---|---|---|
| Brain (10 cases) | AVM | 7 |
| | Left cerebellar mass | 1 |
| | Xanthochromia on lumbar puncture | 1 |
| | Mitochondrial disorder | 1 |
| Abdomen/pelvis (20 cases) | Congenital anomalies | 8 |
| | Liver mass | 3 |
| | Kidney transplant | 3 |
| | DVT | 2 |
| | Acute kidney injury; injury to diaphragm | 2 |
| | Chronic abdominal pain, irritable bowel syndrome | 1 |
| | Suspect small bowel site and vascular malformation | 1 |
| Cardiac (50 cases) | Congenital heart disease | 48 |
| | Heart transplant | 1 |
| | Aortic valve disorders | 1 |
| Extremity (5 cases) | AVM | 5 |
| Spine (1 case) | AVM | 1 |

AVM: arteriovenous malformation; DVT: deep vein thrombosis.